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PARITY, ORAL CONTRACEPTIVES, AND THE RISK OF OVARIAN CANCER AMONG CARRIERS AND NONCARRIERS OF A *BRCA1* OR *BRCA2* MUTATION

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ABSTRACT

Background Multiparity and the use of oral contraceptives reduce the risk of ovarian cancer, but their effects on this risk in women with a *BRCA1* or *BRCA2* mutation are unclear.

Methods We conducted a population-based case–control study of ovarian cancer among Jewish women in Israel. Women were tested for the two founder mutations in *BRCA1* and the one founder mutation in *BRCA2* that are known to be common among Jews. We estimated the effects of parity and oral-contraceptive use on the risk of ovarian cancer in carriers and noncarriers in separate analyses that included all control women, who did not have ovarian cancer.

Results Of 751 controls who underwent mutation analysis, 13 (1.7 percent) had a *BRCA1* or *BRCA2* mutation, whereas 244 of 840 women with ovarian cancer (29.0 percent) had a *BRCA1* or *BRCA2* mutation. Overall, each additional birth and each additional year of use of oral contraceptives were found to lower the risk of ovarian cancer, as expected. Additional births were protective in separate analyses of carriers and noncarriers, but oral-contraceptive use appeared to reduce the risk only in noncarriers; among carriers, the reduction in the odds of ovarian cancer was 12 percent per birth (95 percent confidence interval, 2.3 to 21 percent) and 0.2 percent per year of oral-contraceptive use (−4.9 to 5.0 percent).

Conclusions The risk of ovarian cancer among carriers of a *BRCA1* or *BRCA2* mutation decreases with each birth but not with increased duration of use of oral contraceptives. These data suggest that it is premature to use oral contraceptives for the chemoprevention of ovarian cancer in carriers of such mutations. (N Engl J Med 2001;345:235-40.)

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THE most consistently observed influences on the risk of nonfamilial ovarian cancer are infertility and low parity, which increase the risk, and multiparity and the use of oral contraceptives, which decrease the risk.[1-6] A woman's age at the start and cessation of the use of oral contraceptives and the duration of use are important. The effect of estrogen-replacement therapy on the risk of ovarian cancer is controversial.[1,7-10] Age at first pregnancy is an independent risk factor for breast cancer, but its effect on the risk of ovarian cancer disappears after adjustment for the number of pregnancies.[7] Whether breast-feeding has any effect on the risk is unknown.[6,11,12]

As is true for breast cancer, the cause of ovarian cancer has a familial component. A history of ovarian cancer in two or more first-degree relatives significantly increases the risk of ovarian cancer.[7,13,14] There is also some increase in risk among women whose mothers or sisters had endometrial or breast cancer.[15] A greater proportion of cases of ovarian cancer than of breast cancer is attributable to a *BRCA1* or *BRCA2* mutation.[14,16]

We assessed the effects of parity and the use of oral contraceptives on the risk of ovarian cancer among

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Jewish women in Israel to determine whether the use of oral contraceptives and multiparity lower the risk of ovarian cancer in carriers of a *BRCA1* or *BRCA2* mutation, as they do in noncarriers.

METHODS

Subjects

We identified all Jewish women with pathologically confirmed cancer of the ovary (code 183.0 of the *International Classification of Diseases, 9th Revision, Clinical Modification*) or primary peritoneal carcinoma, possibly of ovarian origin (code 158), diagnosed in Israel between March 1, 1994, and June 30, 1999. To ensure that no patients with newly diagnosed cancer were overlooked, all the departments of gynecology in the country were monitored continually throughout the study and pathology and oncology departments were checked monthly. For each patient, two control women who were matched for age (within two years), area of birth, and place and length of residence in Israel (according to defined categories) were selected from the Central Population Registry. All living subjects gave written informed consent. The study protocol was approved by ethics panels in Israel and the United States.

The patients were interviewed in the hospital, typically four to six days after gynecologic surgery. We attempted to collect a blood sample to test for *BRCA1* and *BRCA2* mutations. Blocks of paraffin-embedded tumor samples were obtained routinely. Midway through the study, we began collecting buccal cells from controls for DNA analysis. The controls were interviewed at home. Interviews were conducted by a group of experienced, multilingual, trained interviewers, and when needed, the interview was conducted in the native language of the respondent.

The interviewers were informed of the goals of the study and taught how to administer the questionnaire and conduct an interview by watching practice interviews. The accuracy and thoroughness of each interviewer were periodically checked to help ensure that the method of data collection was standardized. Family information was validated by reinterviewing a random sample of 7 percent of subjects. To improve the respondents' recall with regard to contraceptive history and to establish the patterns of use, interviewers were asked to relate pill intake to life events.

Laboratory Methods

Subjects were tested for the two common founder mutations in *BRCA1* (185delAG and 5382insC) and the single founder mutation in *BRCA2* (6174delT) as described previously.[17] Briefly, a multiplex polymerase chain reaction was designed to amplify the exons containing the three mutations with the use of fluorescence-labeled primers in a single reaction. Since each mutation is a small insertion or deletion, it can be detected as a length polymorphism with the use of a genetic analyzer (model 310, Applied Biosystems) and Genescan software (Applied Biosystems). Samples known to have mutations were included with each run as controls. Samples available for testing included peripheral blood, paraffin-embedded tissue sections, and buccal cells. DNA was extracted from tissue sections as described previously.[17] Both blood and tissue sections were available for some subjects; the two subjects for whom the results were inconsistent were excluded from the analysis.

Statistical Analysis

We used logistic regression to estimate the effects on the risk of ovarian cancer of having each or any of the three mutations in *BRCA1* and *BRCA2*. We estimated the effects of family history, parity, and oral-contraceptive use in analyses that included all patients, as would be done in a case–control study in which information on genotype was not available. We assessed the effects of parity and oral-contraceptive use further in analyses that included all controls, whether or not genotyping had been performed, but only a subgroup of patients, either patients with a *BRCA1* or *BRCA2* mutation or patients without a *BRCA1* or *BRCA2* mutation. Our approach assumed that carrier status was independent of parity and the use of oral contraceptives in the study population. Accordingly, the best estimates of the distributions of the use of oral contraceptives and parity in subgroups defined according to mutation status among the controls are their distributions among the control subjects as a whole. Restriction of logistic-regression analyses to patients who were carriers and controls who were carriers, the ideal method of assessing effects among carriers, would have left only 13 controls in this study, too few to allow us to estimate effects of parity or the use of oral contraceptives among carriers. A personal history of breast cancer and a family history of breast or ovarian cancer cannot be assumed to be independent of carrier status, because among control subjects a personal history of breast cancer and a history of having first-degree relatives with breast or ovarian cancer should be more frequent among carriers of a *BRCA1* or *BRCA2* mutation than among noncarriers.

All analyses were adjusted for age (in decades); ethnic background (those born in Europe, North or South America, South Africa, or Israel with two parents from these areas are referred to as Ashkenazi; those born in Israel with one parent from the Ashkenazi areas as having mixed ancestry; and all others as non-Ashkenazi); and presence or absence of a personal history of breast cancer (a possible marker for an increased risk of ovarian cancer or a decreased risk as a result of anovulation due to chemical or hormonal treatment), a family history of breast or ovarian cancer (women with a single first-degree relative with breast cancer were considered to be at intermediate risk, and those with one first-degree relative with ovarian cancer or two or more with breast cancer were considered to be at high risk), and a history of gynecologic surgery (tubal ligation, hysterectomy, or unilateral oophorectomy). We also examined the effects of oral-contraceptive use and parity according to mutation status in subgroups categorized according to age (<50 years and ≥ 50 years) and ethnic background (Ashkenazi and non-Ashkenazi) and to the presence or absence of a family history of breast or ovarian cancer and a personal history of breast cancer.

We used the case-only method[18] to test formally whether there was an interaction between carrier status and the use of oral contraceptives and parity. This method also assumes that carrier status and the exposure of interest in the controls are independent; however, it does not allow the effects of oral-contraceptive use and parity to be adjusted for each other or for other risk factors. For some analyses, we used oral-contraceptive use and parity as continuous variables to present the data more simply and to maximize statistical power; reported parity values of more than 10 were coded as 10. Categorical analyses showed similar patterns of risk with respect to parity and the use of oral contraceptives.

RESULTS

During the five-year study period, 1707 Jewish women were given a diagnosis of ovarian cancer in Israel. Of these women, 1695 (99.3 percent) had pathology reports available; 1226 (71.8 percent of the total) had invasive epithelial carcinoma, 100 (5.9 percent) had invasive peritoneal carcinoma, 263 (15.4 percent) had borderline histologic findings indicating that the lesion had a low malignant potential, and 106 (6.2 percent) had cancers of nonepithelial origin. Of the 1326 women with peritoneal or epithelial cancer, 1124 (84.8 percent) were interviewed, 68 died before we could interview them, 48 were too sick to be interviewed, 86 did not consent to be interviewed, and 9 were subsequently excluded because they reported having undergone a bilateral oophorectomy. The number of cases of ovarian cancer was approximately equal in each year of the study.

Molecular analysis for founder mutations in *BRCA1*

or *BRCA2* was completed successfully in 840 of the 1115 women with peritoneal or epithelial cancer (75.3 percent) who were interviewed.

We interviewed 2397 of the 3567 controls (67.2 percent) whom we contacted. We excluded 128 controls who reported undergoing bilateral oophorectomy. Of the 968 control women from whom we attempted to collect buccal cells, we successfully tested 751 for mutations (77.6 percent).

Table 1 shows the characteristics of the patients in whom mutation testing was completed, according to age, ethnic background, and presence or absence of a family history of breast or ovarian cancer. Over half the patients were 60 years of age or older and over 70 percent were classified as Ashkenazi. In the early stages of the study, patients with a family history of breast or ovarian cancer were slightly more likely to have been analyzed for a *BRCA1* or *BRCA2* mutation.[16] There were no significant differences in the age at diagnosis and ethnic origin between patients who underwent mutation analysis and those who did not undergo testing.

Overall, 29.0 percent of patients and 1.7 percent of controls who underwent mutation analysis had a founder mutation in *BRCA1* or *BRCA2* (Table 2). The prevalence of mutations among patients with invasive epithelial ovarian cancer was very similar to that among those with invasive peritoneal cancer, but it was only 4.3 percent in the group of women with borderline histologic findings (data not shown). Therefore, in further analyses we included only the 840 women with invasive epithelial or peritoneal cancer who underwent mutation analysis.

Table 3 shows the effects of parity and oral-contraceptive use on the risk of ovarian cancer among the women who underwent mutation analysis. Similar results were obtained in analyses that included all women (data not shown). There was a significant decrease in risk among women with increasing parity and in those who had used oral contraceptives for five or more years.

Table 4 shows the effect of the use of oral contraceptives on the risk of ovarian cancer for patients with a *BRCA1* or *BRCA2* mutation and for patients with no *BRCA1* or *BRCA2* mutation, as compared with the entire control group. Although oral-contraceptive use was associated with a significant decrease in risk among patients without a *BRCA1* or *BRCA2* mutation, it had no protective effect among women with a *BRCA1* or *BRCA2* mutation. Increasing parity had a protective effect in both groups of women.

In continuous analyses, which may be more powerful and can be more informative in the case of individual analyses, the relative risk among all women was reduced by 3.5 percent (95 percent confidence interval, 0.1 to 6.8 percent) for each year of oral-contraceptive use. The reduction in risk was limited to women who did not have a *BRCA1* or *BRCA2* mutation (5.8 percent; 95 percent confidence interval, 1.5 to 10 percent); there was no apparent reduction in risk with oral-contraceptive use among the carriers (0.2 percent for each year of use; 95 percent confidence interval,

TABLE 1. CHARACTERISTICS OF THE WOMEN WITH OVARIAN CANCER, ACCORDING TO WHETHER THEY UNDERWENT MUTATION ANALYSIS.

CHARACTERISTIC	DECLINED TESTING (N=224)	NO SPECIMEN AVAILABLE (N=51)	TESTED (N=840)	TOTAL (N=1115)
		no. of women (%)		
Age				
<40 yr	15	2	31 (64.6)	48
40–49 yr	38	4	163 (79.5)	205
50–59 yr	50	5	205 (78.8)	260
60–69 yr	71	12	244 (74.6)	327
≥70 yr	50	28	197 (71.6)	275
Ethnic background*				
Ashkenazi	151	37	601 (76.2)	789
Non-Ashkenazi	59	13	193 (72.8)	265
Mixed ancestry	14	1	46 (75.4)	61
History of breast or ovarian cancer in ≥1 first-degree relative				
None	204	45	716 (74.2)	965
1 with breast cancer	13	6	70 (78.7)	89
>1 with breast cancer or ≥1 with ovarian cancer	7	0	54 (88.5)	61

*Women born in Europe, North or South America, South Africa, or Israel with two parents from these areas are referred to as Ashkenazis; those born in Israel with one parent from the Ashkenazi areas as having mixed ancestry; and all others as non-Ashkenazi.

TABLE 2. EFFECT OF A FOUNDER MUTATION IN *BRCA1* OR *BRCA2* ON THE RISK OF OVARIAN CANCER.

MUTATION	PATIENTS (N=840)	CONTROLS (N=751)	ODDS RATIO (95% CI)*
	no. (%)		
No mutation†	596 (71.0)	738 (98.3)	1.0
BRCA1			
185delAG	162 (19.3)	2 (0.3)	106 (26–427)‡
5382insC	20 (2.4)	1 (0.1)	25 (3.3–187)‡
BRCA2			
6174delT	64 (7.6)	10 (1.3)	7.9 (4.0–16)
Any mutation§	244 (29.0)	13 (1.7)	24 (14–43)

*Values were adjusted for ethnic background (Ashkenazi or non-Ashkenazi) and age (in decades). CI denotes confidence interval.

†This group served as the reference group.

‡Estimates of the odds ratios and confidence intervals are unreliable because of the small numbers of subjects.

§One patient had both the 185delAG mutation in *BRCA1* and the 6174delT mutation in *BRCA2;* another had both the 5382insC mutation in *BRCA1* and the 6174delT mutation in *BRCA2.* None of the controls had more than one mutation.

TABLE 3. EFFECT OF PARITY AND USE OF ORAL CONTRACEPTIVES ON THE RISK OF OVARIAN CANCER.*

VARIABLE	PATIENTS (N=832)	CONTROLS (N=2257)	ODDS RATIO (95% CI)†
	no. (%)		
No. of births			
0‡	88 (10.6)	161 (7.1)	1.0
1–2	367 (44.1)	998 (44.2)	0.56 (0.42–0.77)
3–4	289 (34.7)	820 (36.3)	0.53 (0.39–0.73)
≥5	88 (10.6)	278 (12.3)	0.47 (0.32–0.69)
Duration of oral-contraceptive use			
0 yr‡	678 (81.5)	1740 (77.1)	1.0
0.1–1.9 yr	69 (8.3)	171 (7.6)	1.15 (0.84–1.57)
2.0–4.9 yr	42 (5.0)	154 (6.8)	0.77 (0.53–1.12)
≥5.0 yr	43 (5.2)	192 (8.5)	0.69 (0.48–0.98)

*The analysis included 832 patients with epithelial or peritoneal carcinoma who underwent mutation analysis and 2257 controls, whether or not they underwent mutation analysis. Eight patients and 11 controls whose personal history of breast cancer was unknown and 1 control whose parity was unknown were excluded.

†The estimates were adjusted for the other listed variable; age; presence or absence of a family history of breast or ovarian cancer, a personal history of breast cancer, or a history of gynecologic surgery; and ethnic background. CI denotes confidence interval.

‡This group served as the reference group.

−4.9 to 5.0 percent). By contrast, the reduction in risk for each additional birth was greater in carriers (12 percent; 95 percent confidence interval, 2.3 to 21 percent) than in noncarriers (6.0 percent; 95 percent confidence interval, 1.0 to 11 percent).

In the analysis of the interactions between carrier status and the reproductive factors (see Supplementary Appendix 1, available with the complete text of this article at http://www.nejm.org), oral-contraceptive use had less of a protective effect in carriers of a *BRCA1* or *BRCA2* mutation than in noncarriers, but increasing parity had a greater protective effect. The small number of patients who had a *BRCA2* mutation suggests that they are protected by oral-contraceptive use (odds ratio, 0.95 per year of use; 95 percent confidence interval, 0.84 to 1.08), whereas the large number of patients with a *BRCA1* mutation suggests that they are not so protected, but the difference could also be due to chance (Supplementary Appendix 1).

When we examined subgroups of carriers, we found some evidence that oral-contraceptive use was protective in older women (odds ratio, 0.97 per year of use; 95 percent confidence interval, 0.90 to 1.04). These women would have been more likely than younger women to have used the high-dose pills common in the 1960s and 1970s.

DISCUSSION

Our findings show that the use of oral contraceptives and increasing parity protect against ovarian cancer in Israel, as they do in other countries.[19,20] We failed, however, to find clear evidence of a protective effect of oral-contraceptive use among women who had a founder mutation in *BRCA1* or *BRCA2;* by contrast, increasing parity was protective in both carriers and noncarriers.

We identified as carriers 244 of 840 patients with ovarian cancer (29.0 percent). This high prevalence enabled us to investigate whether the factors that have been established as protective in the general population were also protective in carriers. However, the low frequency of oral-contraceptive use and *BRCA1* or *BRCA2* mutations among the controls precludes us from drawing definitive conclusions, since our study lacked the statistical power to allow us to assess effects in carriers alone or to estimate the interaction between heredity and environmental factors using all the data. This problem forced us to rely on nonstandard statistical techniques.

The precision of our estimates is less than suggested by the confidence intervals if there is, in fact, any uncertainty about the assumption that the use of oral contraceptives and parity are independent of carrier status among Israeli women.[21] Furthermore, since the case-only analysis[18] does not take demographic or additional reproductive factors into account, distortion of the estimate of interaction is possible. Despite these difficulties, we believe that our study provides substantial evidence that the effects of the use of oral contraceptives differ between women with a *BRCA1* or *BRCA2* mutation and those without a *BRCA1* or *BRCA2* mutation.

Contrary to our results, Narod et al. reported that

TABLE 4. EFFECT OF PARITY AND USE OF ORAL CONTRACEPTIVES ON THE RISK OF OVARIAN CANCER, ACCORDING TO MUTATION STATUS.*

VARIABLE	CONTROLS (N=2257)	CARRIERS		NONCARRIERS	
		PATIENTS WITH MUTATIONS (N=240)	ODDS RATIO (95% CI)†	PATIENTS WITHOUT MUTATIONS (N=592)	ODDS RATIO (95% CI)†
	no. (%)	no. (%)		no. (%)	
No. of births					
0‡	161 (7.1)	20 (8.3)	1.0	68 (11.5)	1.0
1–2	998 (44.2)	119 (49.6)	0.74 (0.42–1.30)	248 (41.9)	0.52 (0.37–0.73)
3–4	820 (36.3)	90 (37.5)	0.69 (0.39–1.23)	199 (33.6)	0.48 (0.34–0.68)
≥5	278 (12.3)	11 (4.6)	0.38 (0.17–0.88)	77 (13.0)	0.48 (0.32–0.71)
Duration of oral contraceptive use					
0 yr‡	1740 (77.1)	184 (76.7)	1.0	494 (83.4)	1.0
0.1–1.9 yr	171 (7.6)	22 (9.2)	1.14 (0.67–1.94)	47 (7.9)	1.13 (0.79–1.62)
2.0–4.9 yr	154 (6.8)	15 (6.2)	0.77 (0.41–1.44)	27 (4.6)	0.74 (0.48–1.16)
≥5.0 yr	192 (8.5)	19 (7.9)	1.07 (0.63–1.83)	24 (4.1)	0.53 (0.34–0.84)

*Carrier and noncarrier controls as well as those who did not undergo mutation analysis were included in the analysis, as explained in the Methods section. Only patients who underwent mutation analysis were included in the analysis. Eight patients (4 in each group) and 11 controls whose personal history of breast cancer was unknown and 1 control whose parity was unknown were excluded.

†The odds ratios are for the comparison with the control group as a whole. The estimates were adjusted for the other variable; age; presence or absence of a family history of breast or ovarian cancer, a personal history of breast cancer, or a history of gynecologic surgery; and ethnic background. CI denotes confidence interval.

‡This group served as the reference group for each comparison.

the use of oral contraceptives had a protective effect in women with a *BRCA1* or *BRCA2* mutation.[22] The discrepancy could be due to differences between a population-based and a clinic-based setting, to different methods, or to chance. We could compare the risk in carriers who used oral contraceptives with the risk in noncarriers because we studied all Jewish Israeli women who had ovarian cancer. By contrast, Narod et al.[22] studied mainly women from high-risk families, many of whom had undergone prophylactic oophorectomy. Only additional research can resolve the discrepancy.

The reduction in the risk of ovarian cancer associated with multiparity and the use of oral contraceptives has variously been interpreted as a consequence of fewer ovulations,[23] less stimulation of the ovary by gonadotropin,[24] or progestin-induced apoptosis.[25,26] There is no obvious reason for a *BRCA1* or *BRCA2* mutation to influence these effects of oral contraceptives. If, indeed, such mutations do change the effects of oral-contraceptive use and parity, we should look for other differences between carriers and noncarriers in the pathways to ovarian cancer.

There have been reports that oral-contraceptive use has a differential effect on the risk of breast cancer in women with a *BRCA1* or *BRCA2* mutation[27] and in women at high risk because of a family history of the disease.[28] Results from a prevention trial of tamoxifen therapy suggest that among the women who were most likely to have a *BRCA1* or *BRCA2* mutation, the risk of breast cancer was higher among those who were taking the drug than among those who were not taking the drug.[29] Together with our data, these results necessitate caution in the use of an approach that bases the need for chemoprevention on factors known to be effective only in noncarriers or in a population that includes both carriers and noncarriers.

Our findings demonstrate the difficulty of assessing the joint effects of a rare genetic factor and environmental factors, even in a large study of a disease that is strongly associated with highly penetrant mutations in a population where such mutations are common. We believe that it is premature to prescribe oral contraceptives for the chemoprevention of ovarian cancer in carriers of a *BRCA1* or *BRCA2* mutation, particularly in the light of the report of a possible increased risk of breast cancer in such women.[29]

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This article is dedicated to the memory of Michaela Modan.

APPENDIX

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